

Genomics and precision medicine

Apply Genomics to Precision Medicine

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*TRACO
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Outline

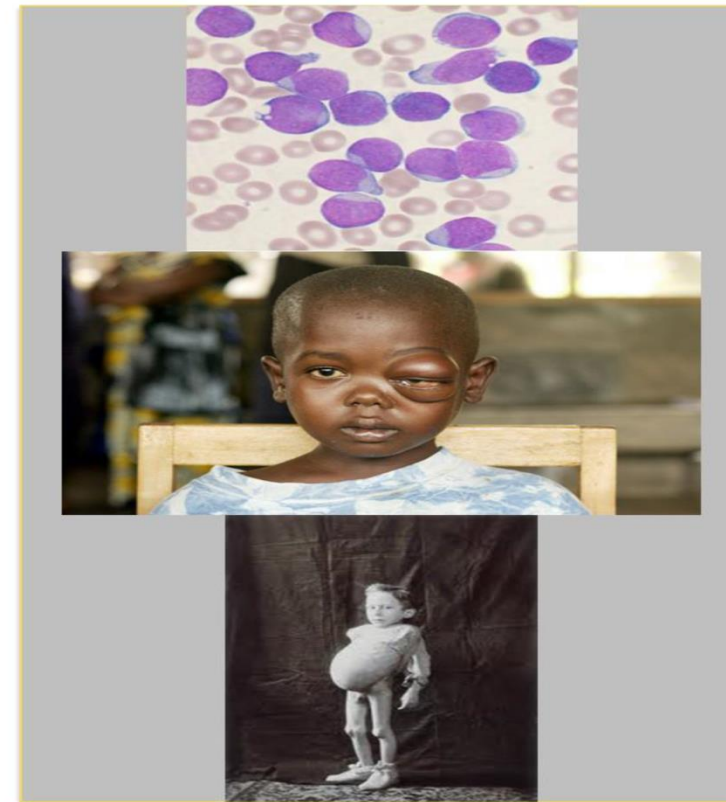
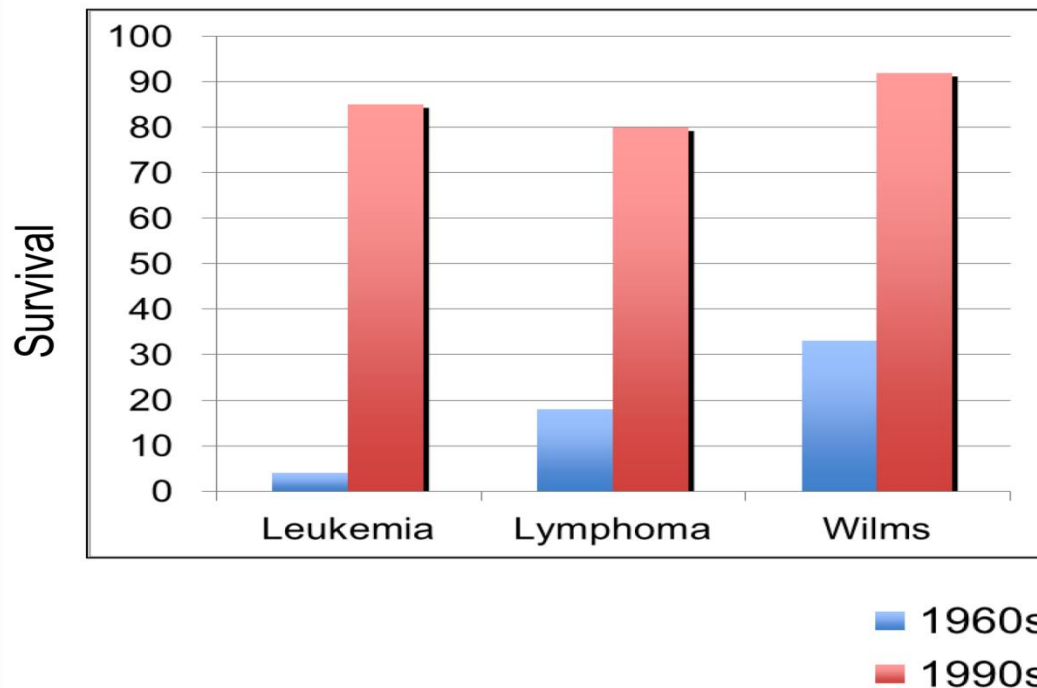
Outline

- **Success and Challenges of Treating Pediatric Cancers**
- **Genomics**
- **Next-generation Sequencing**
- **Application of next-generation sequencing:**
 - **Diagnosis**
 - **Identification of molecular target**
- **Precision Therapy**

Childhood cancer

National Cancer Institute

Childhood cancer: The beginning of a modern medical success story

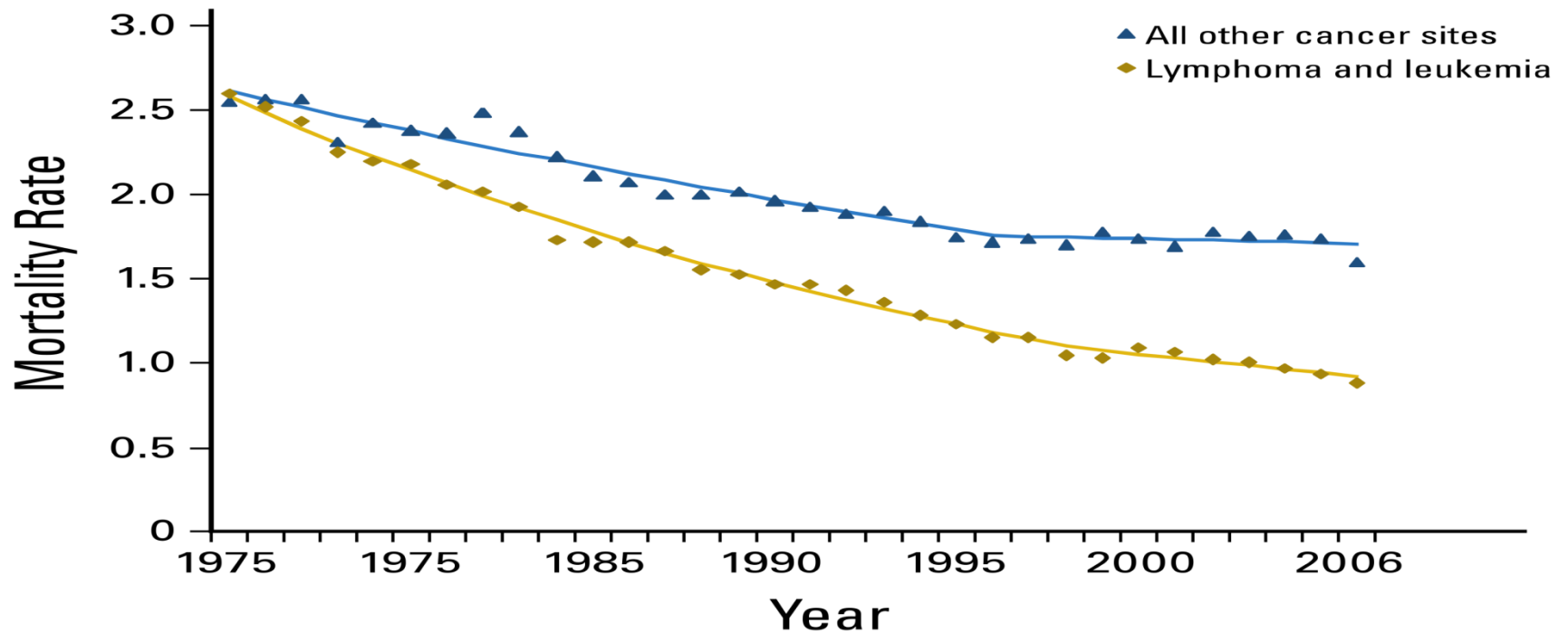


Courtesy: John Maris

Mortality rates

National Cancer Institute

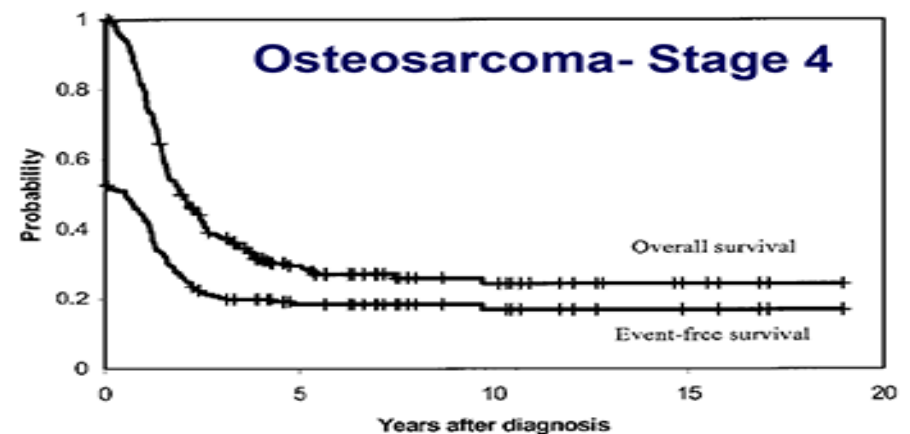
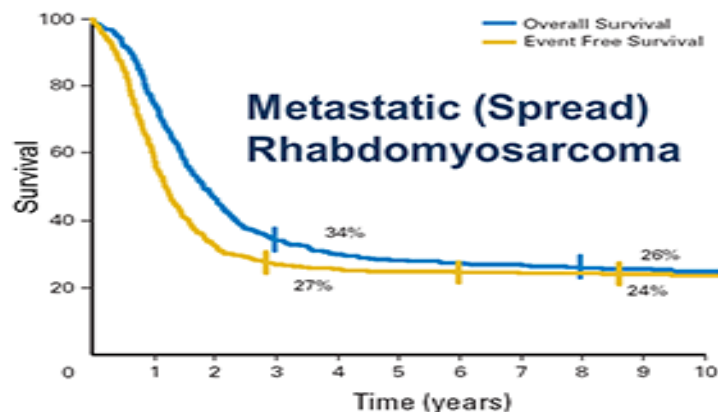
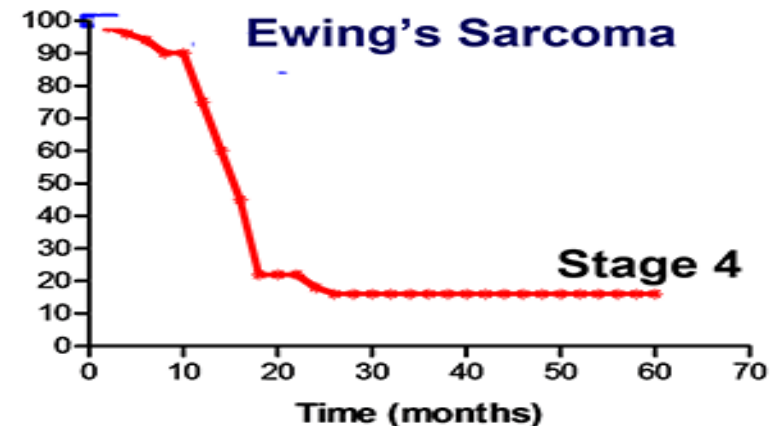
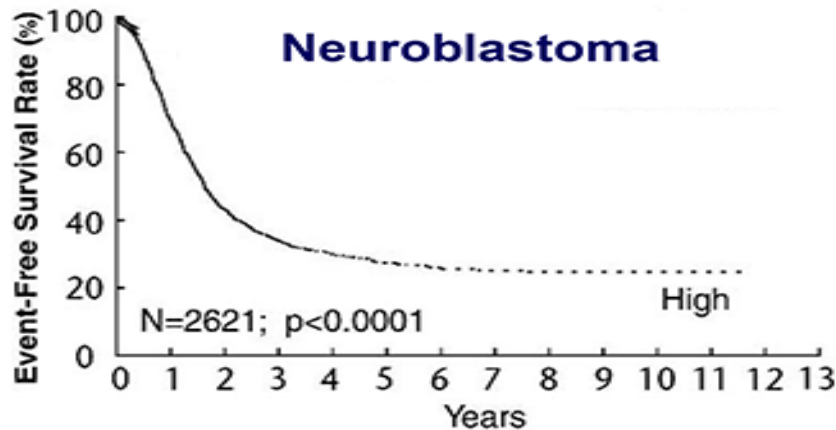
However in the past 16 years no improvement in mortality rates despite increased intensity of treatment



Courtesy: Malcolm Smith

Pediatric cancers

Metastatic, Recurrent, & Refractory Disease Remains Incurable



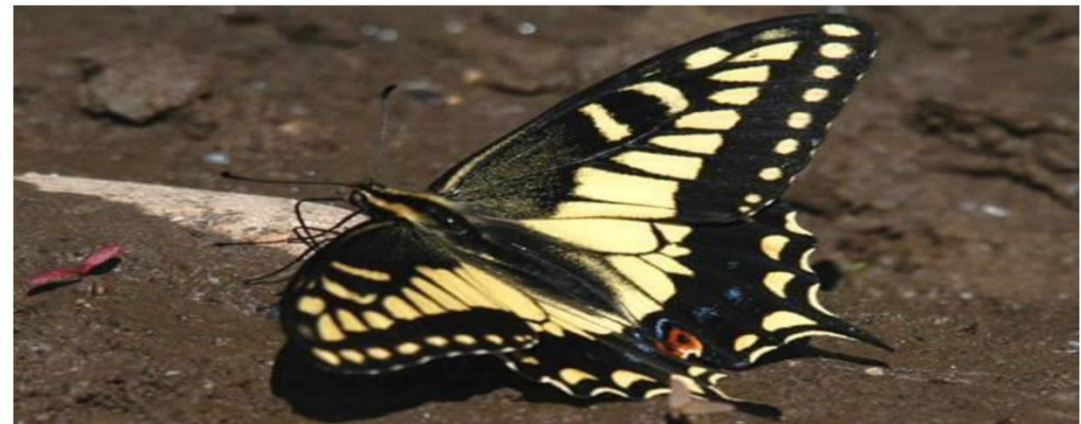
Gene expression

The dramatic consequences of gene expression in biology



Anise swallowtail, *Papilio zelicaon*

Same genome →
Different expression pattern
Different proteome
Different tissues
Different physiology

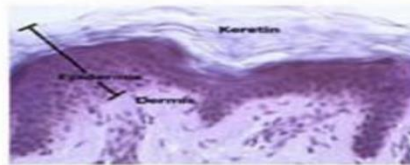


Gene expression

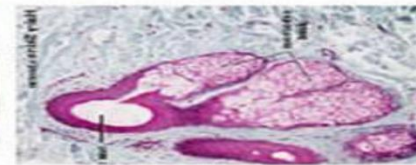
...but the complexity and diversity

Same genome or DNA →

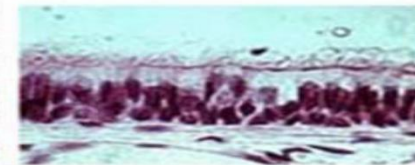
- Different expression pattern
 - Different proteome
 - Different tissues
- Different physiology



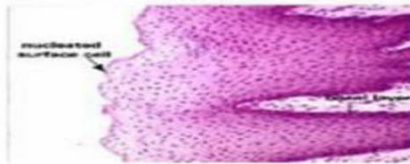
skin



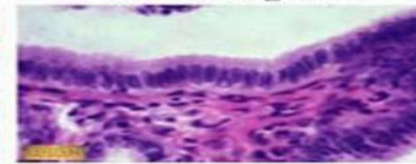
sebaceous gland



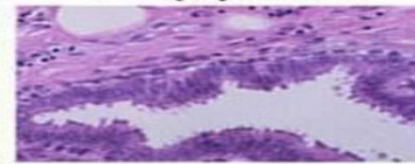
airway epithelium



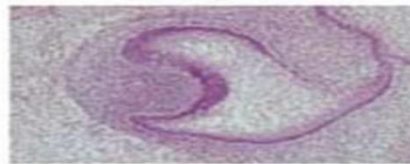
tongue



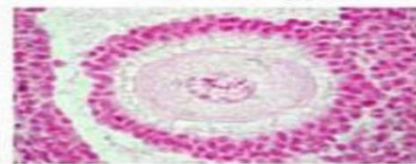
intestinal crypt



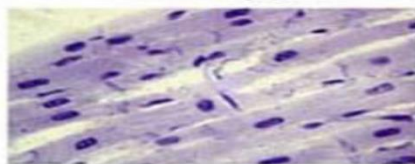
mammary gland



developing tooth



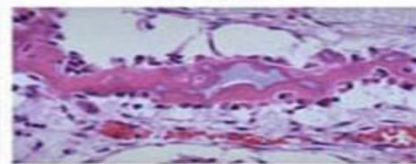
follicle



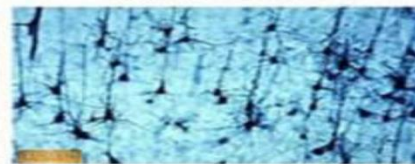
skeletal muscle



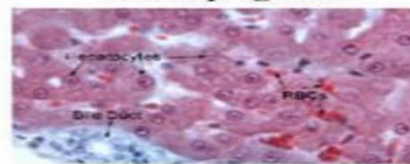
developing bone



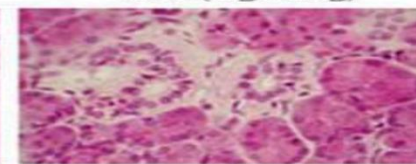
bone (high mag)



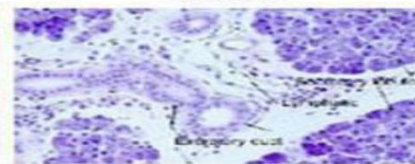
neuron



liver



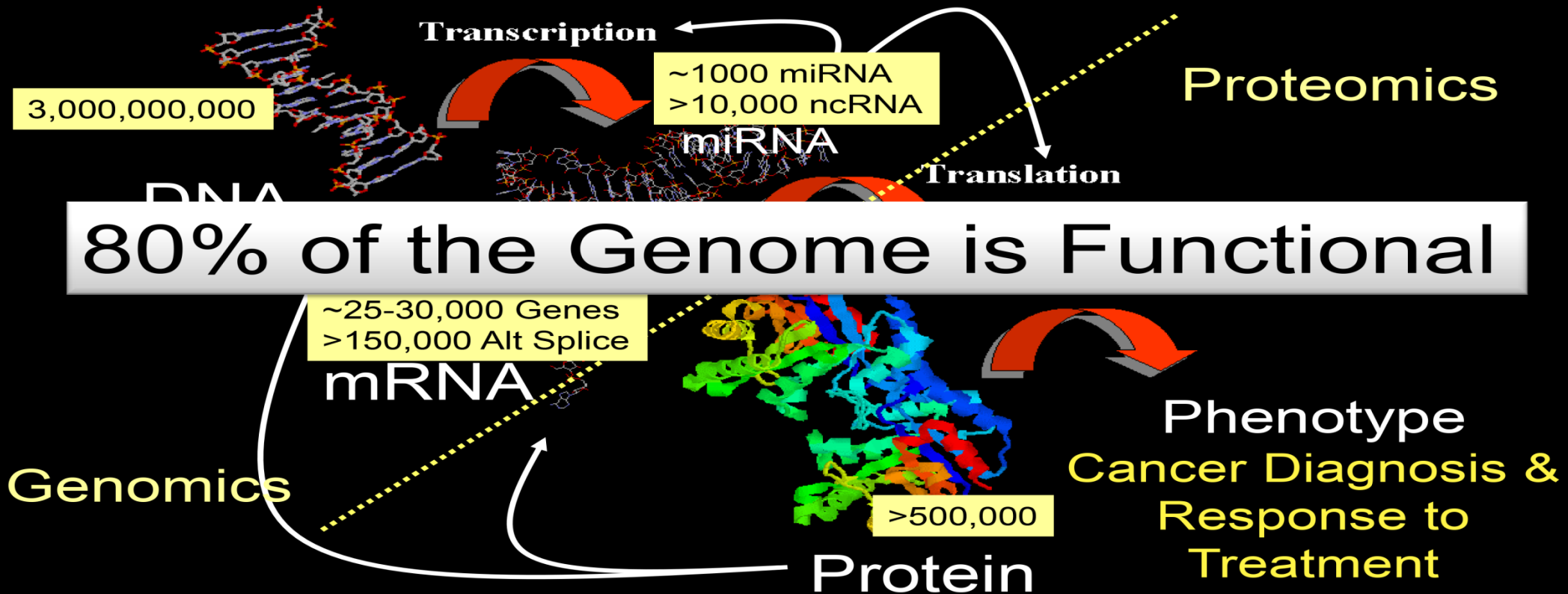
pancreas



parathyroid gland

Gene expression

Biology is driven by the simultaneous expression of large numbers of genes acting in concert

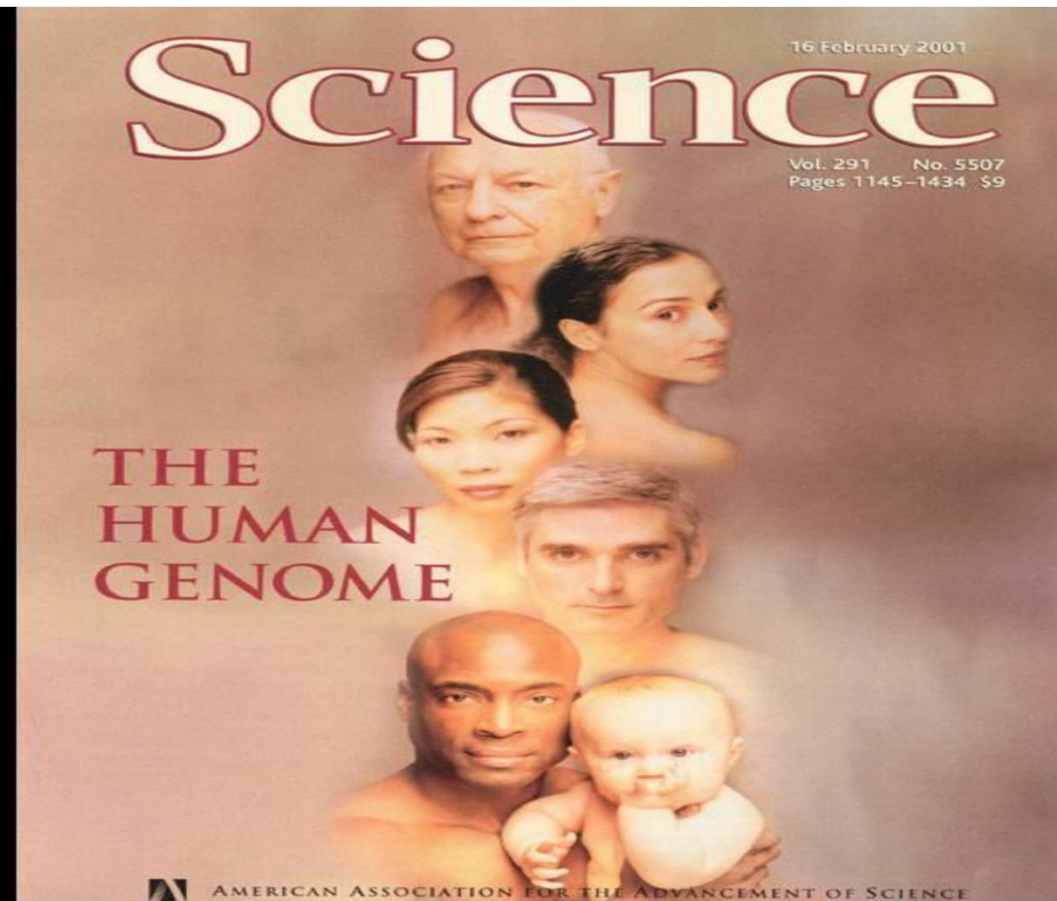


Gene measurement

Challenge: how to measure/detect genes and their products in a massively parallel way?

- **High-throughput technologies**
- **Computational power**

Human genome



Microarrays

1st generation genomic tool: microarrays

Printing microarrays

Mechanical

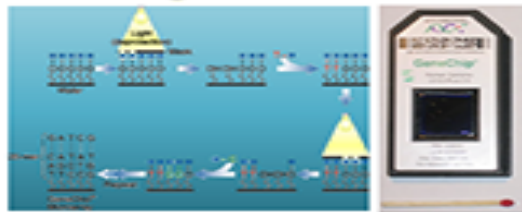


Electronic Piezo

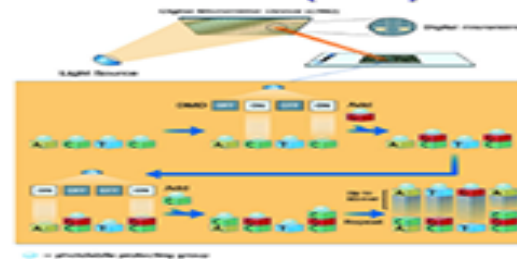


In-situ synthesis microarrays

**Lithographic masks
and de-protection
through illumination**



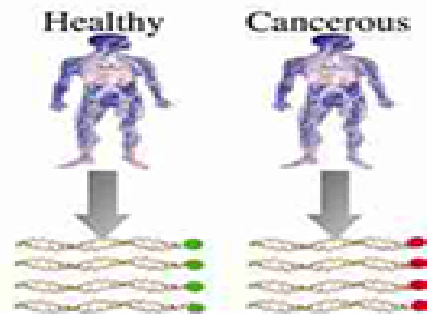
**Digital micromirror
device (DMD)**



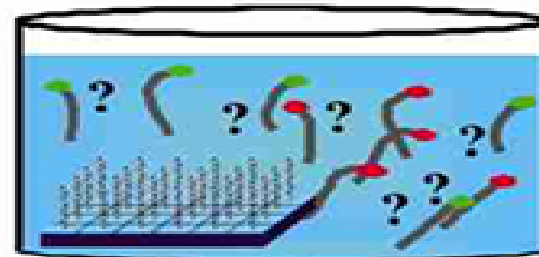
Technologies of hybridization

Microarrays – technologies of hybridization

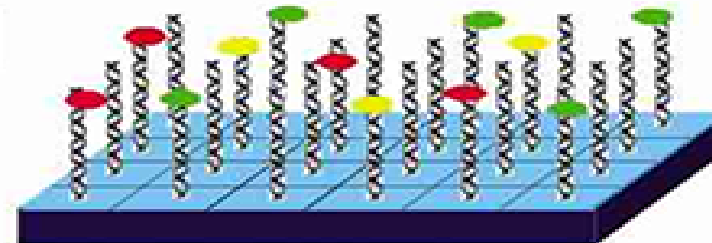
1) Targets are isolated and labeled



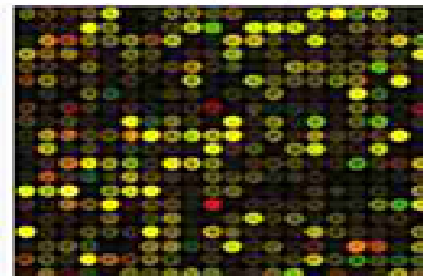
2) Labeled targets are combined with array



3) Array is washed after hybridization*



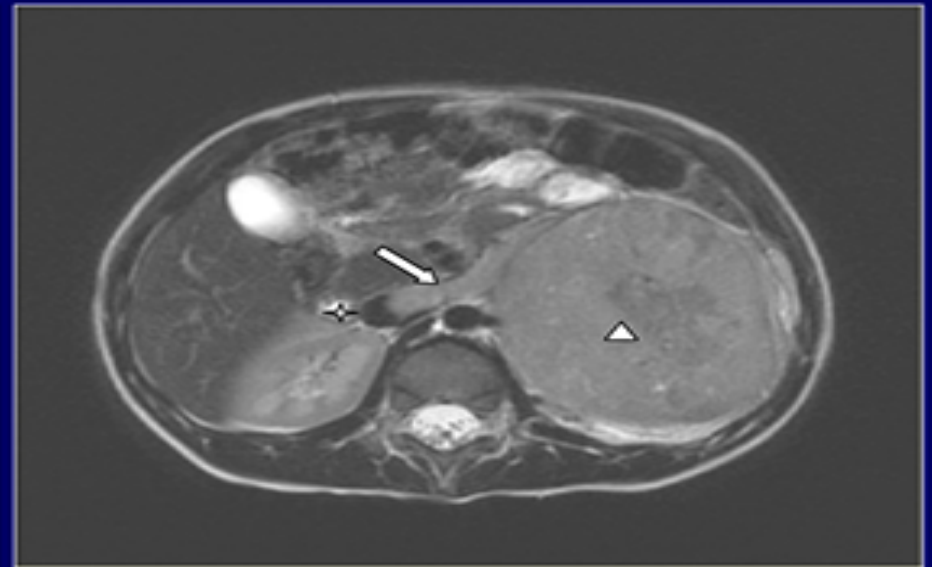
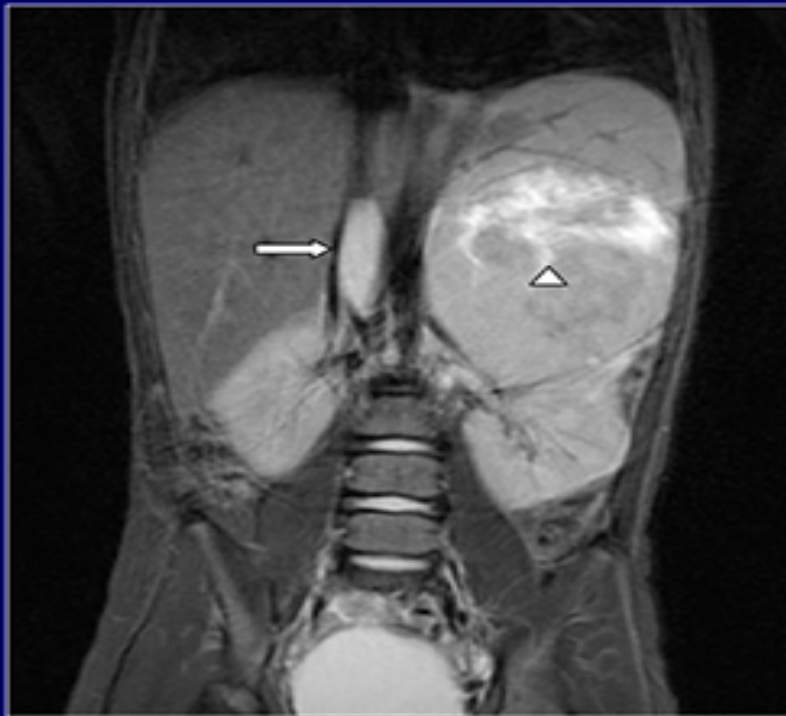
4) Hybridized array is scanned



Clinical vignette

Clinical Vignette

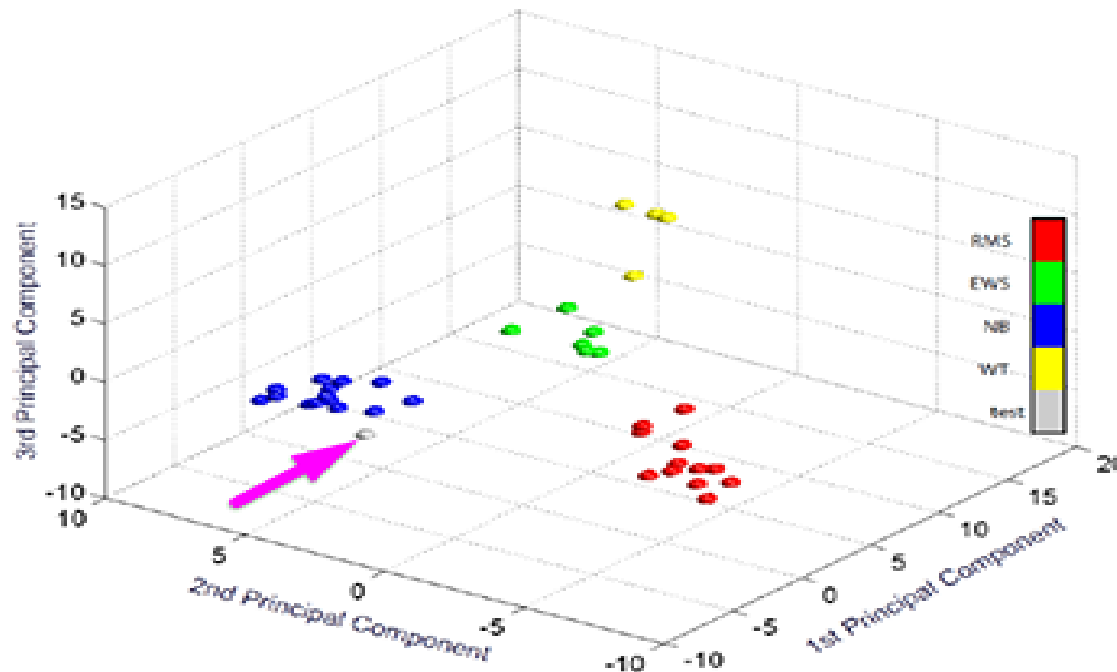
MRI:
9 x 8 x 9 cm
mass in
upper pole
left kidney,
tumor in
Left renal
vein and
inferior
vena cava



Wilm's tumor?

Cancer diagnosis

Diagnosis of cancers using gene expression profiles derived from DNA microarrays



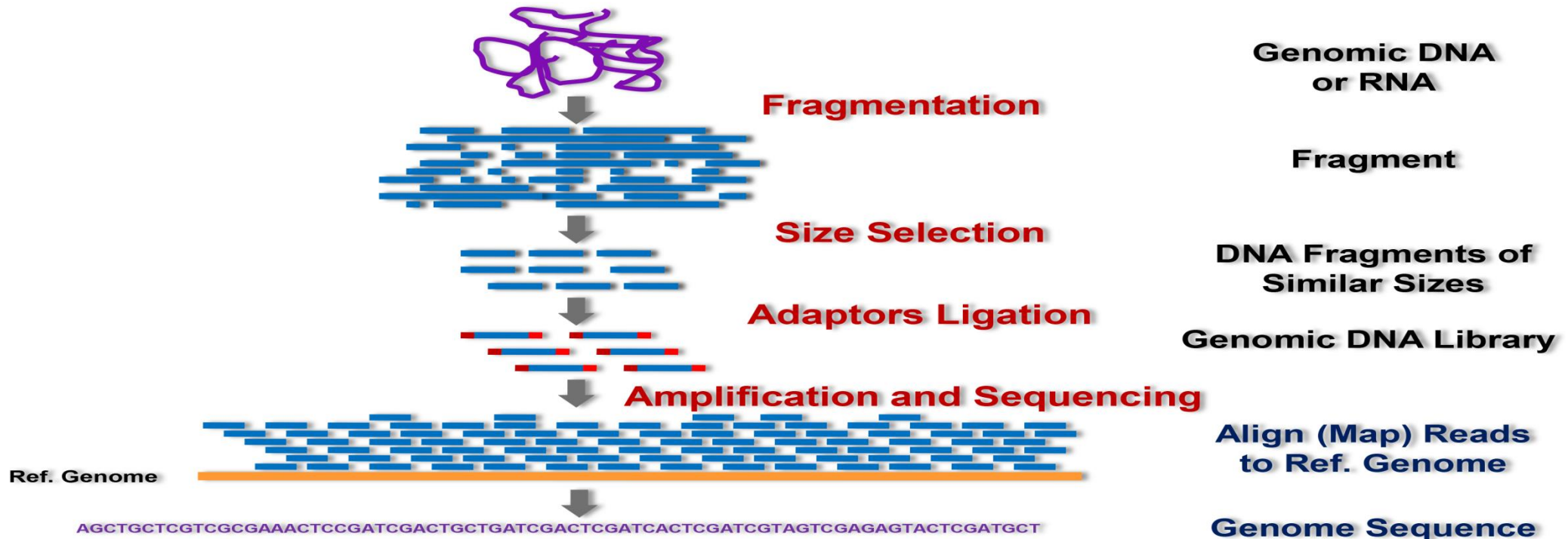
Wilm's tumor



Neuroblastoma

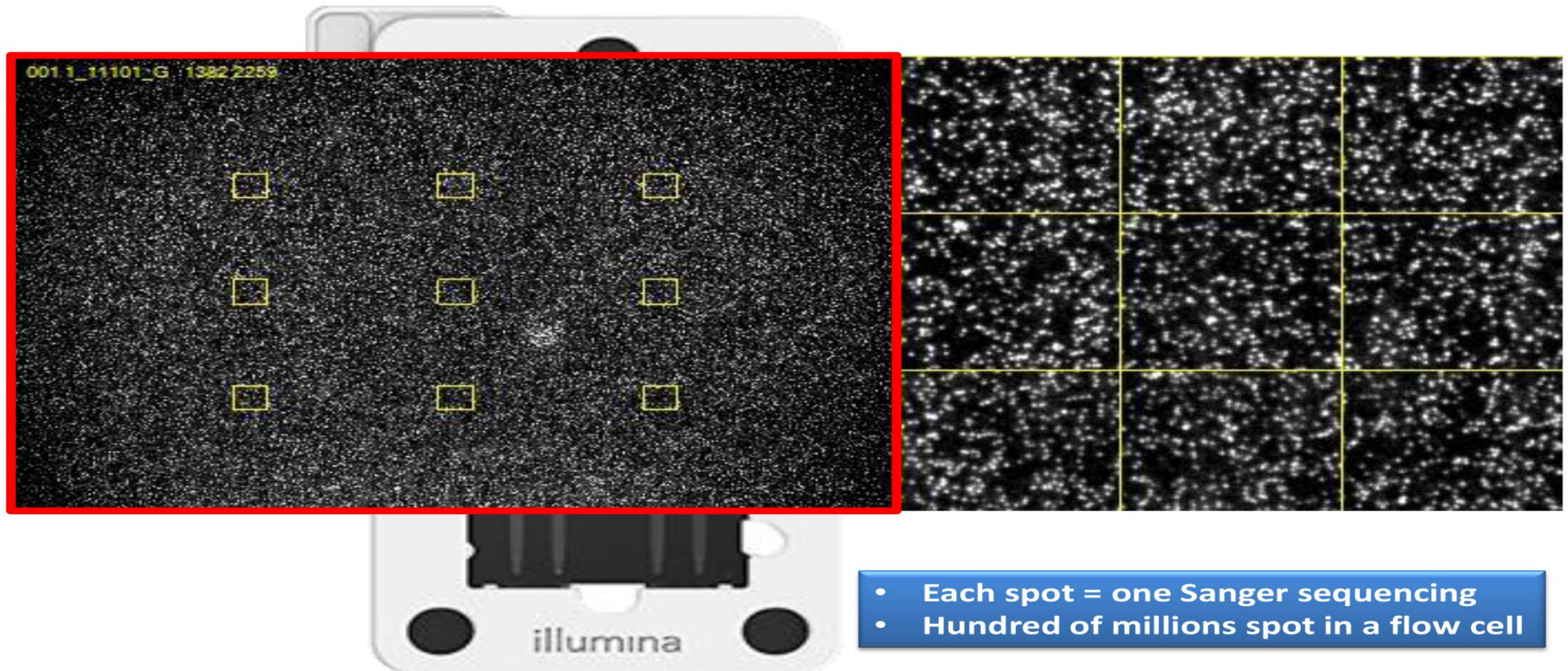
Next-generation sequencing

Next-Generation Sequencing



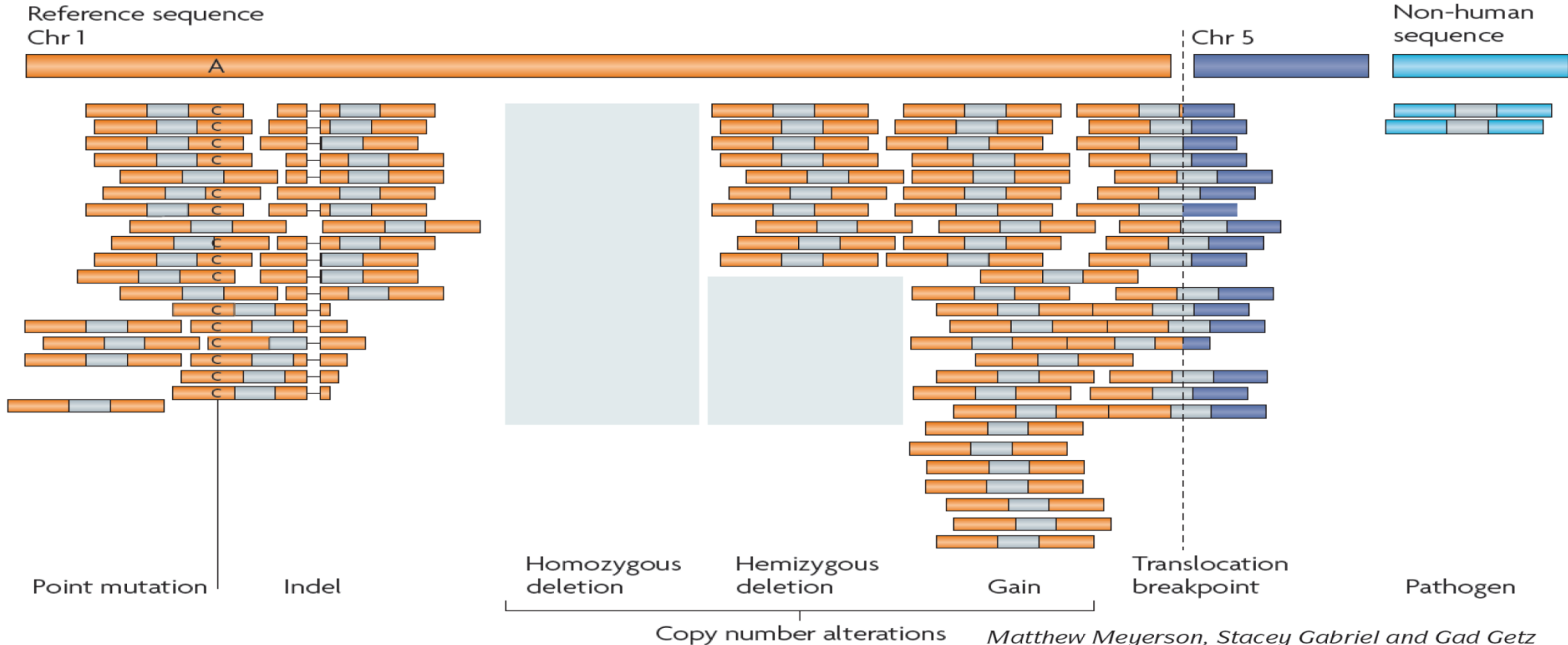
Massively Parallel Sequencing

Massively Parallel Sequencing



Genomic Alterations

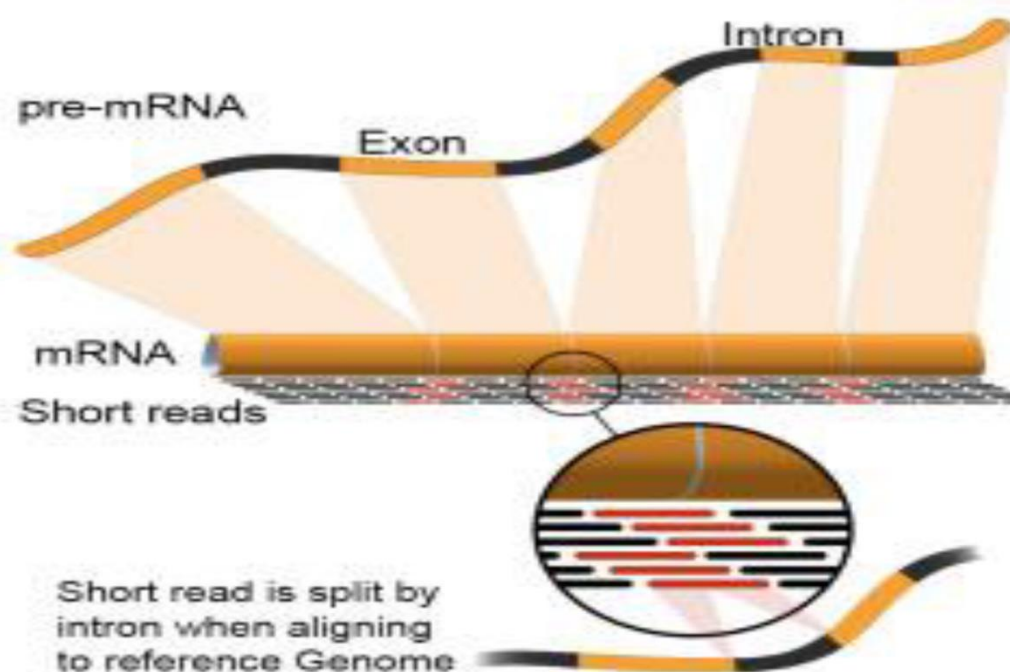
Genomic alterations detected by DNA sequencing



Genomic Alterations in Cancer

GenomeClinomics for precision medicine

Genomic Alterations Detected by RNA Transcriptome Sequencing



- Digital Gene Expression
- Expressed Mutations
- Alternative Splicing Events
- Expressed Fusion Transcripts
- RNA editing
- Novel Transcripts
- Non-coding RNAs

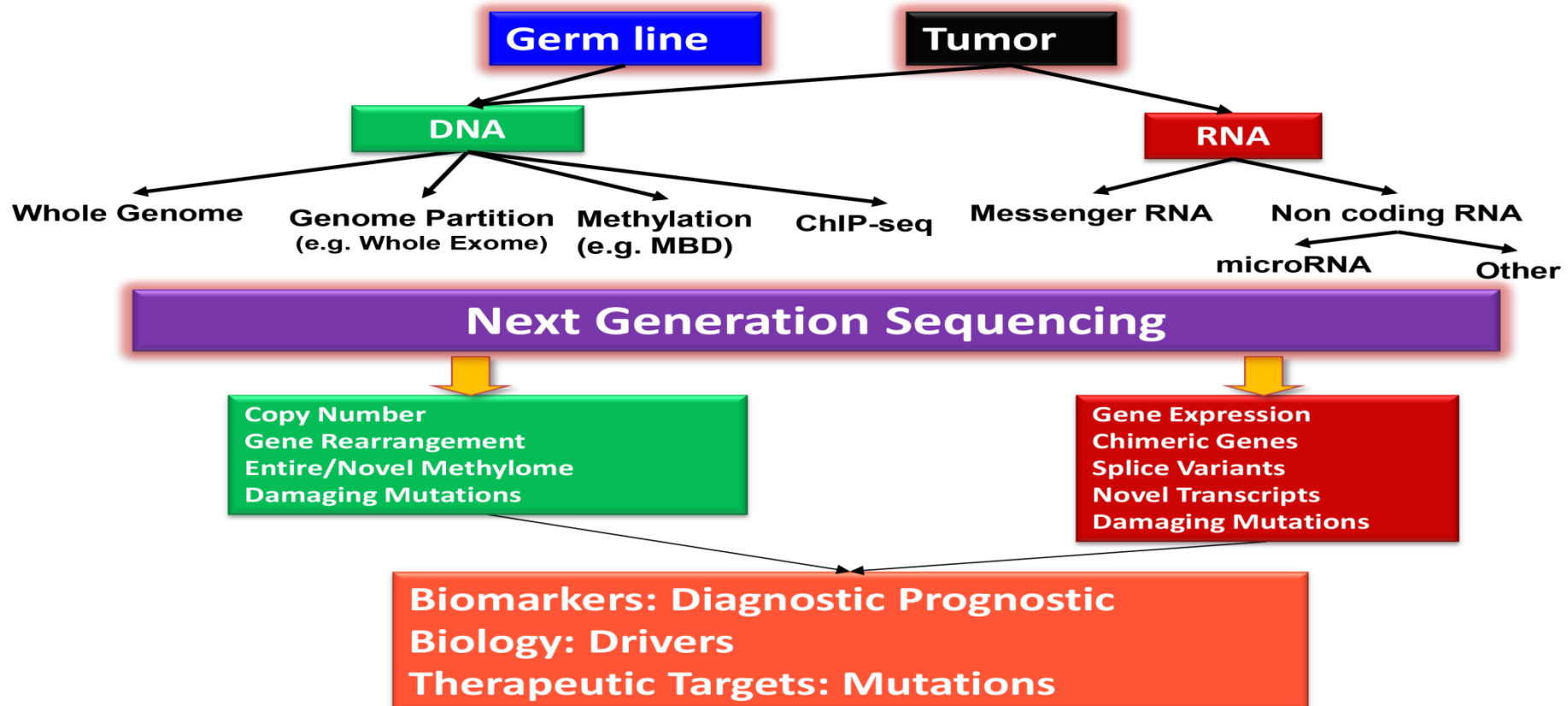
Properties

Properties of the next-generation sequencing technologies

- No need to prepare clones for DNA fragments
- No need of prior knowledge for probe design
- Able to detect balanced genome structure changes
- Parallel sequencing at basepair resolution—massive-throughput (up to 100s Gb/run)
- Cheaper (per nucleotide) and faster per genome

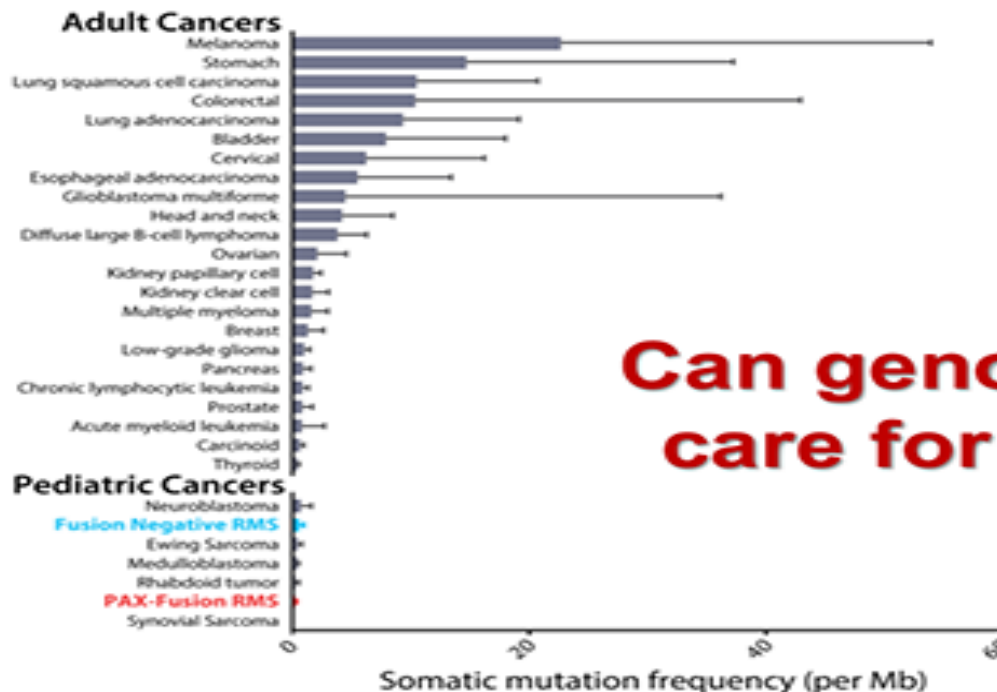
Cancer Genomes

Next Generation Sequencing Allows for Comprehensive Analysis of Cancer Genomes on the Same Platform



Pediatric cancer mutations

Pediatric Cancers Have A Low Number of Somatic and Actionable Mutations At Initial Diagnosis



Can genomics help clinical care for cancer patients?

ClinOmics Program

ClinOmics Program – Multidimensional Integrated Clinical Omics Platform for all patients at CCR

Personalized Medicine and Imaging

Clinical
Cancer
Research

MultiDimensional ClinOmics for Precision Therapy of Children and Adolescent Young Adults with Relapsed and Refractory Cancer: A Report from the Center for Cancer Research

Wendy Chang^{1,2,3}, Andrew S. Brohl^{1,4}, Rajesh Patidar¹, Sivasish Sindiri¹, Jack F. Shern^{1,2}, Jun S. Wei¹, Young K. Song¹, Marielle E. Yohe^{1,2}, Berkley Gryder¹, Shile Zhang¹, Kathleen A. Calzone⁵, Nityashree Shivaprasad¹, Xinyu Wen¹, Thomas C. Badgett^{1,6}, Markku Miettinen⁷, Kip R. Hartman^{8,9}, James C. League-Pascual^{2,8}, Toby N. Trahair¹⁰, Brigitte C. Widemann², Melinda S. Merchant², Rosandra N. Kaplan², Jimmy C. Lin¹, and Javed Khan¹

Clin Cancer Res. 2016 Aug 1;22(15):3810-20

Study design

Study Design

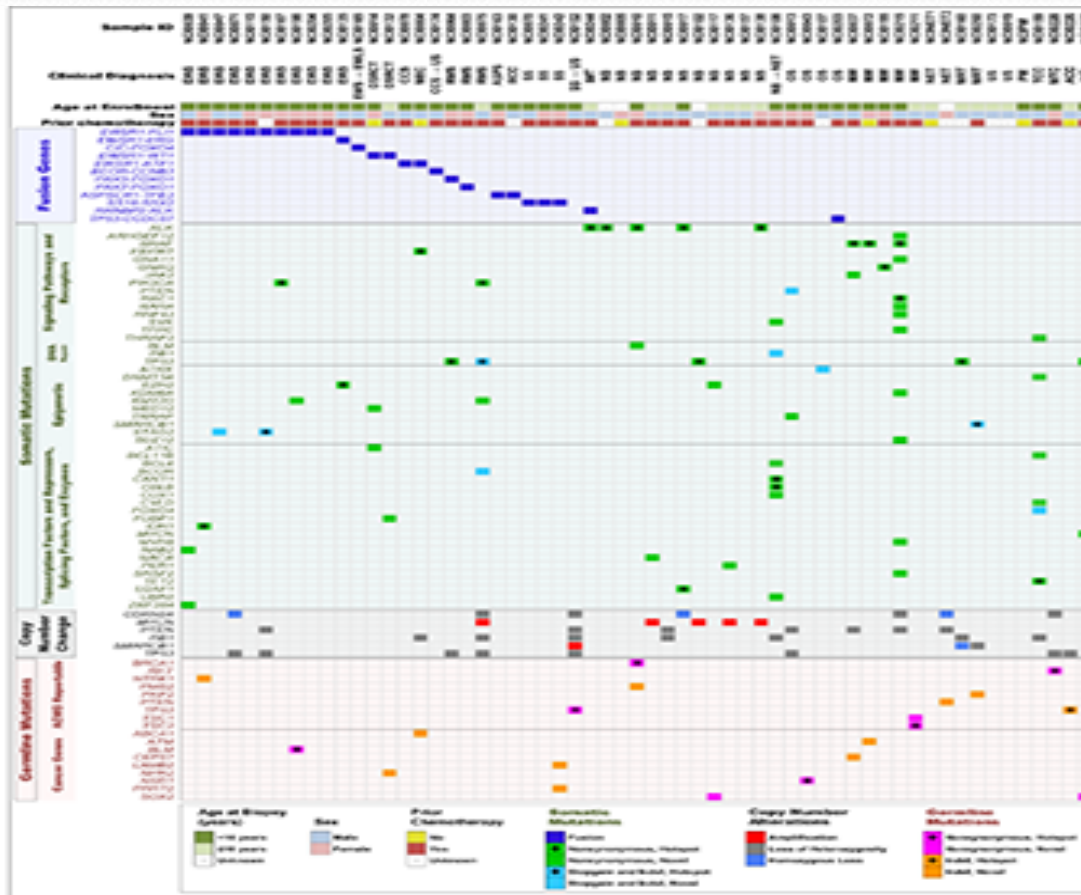
- Pilot study to determine the utility and feasibility of performing comprehensive genomic analyses to identify clinically actionable mutations in pediatric and young adult patients with metastatic, refractory or relapsed solid tumors
- 59 patients enrolled to Omics protocol (10-C-0086) at the Pediatric Oncology Branch, Center for Cancer Research (CCR), NCI (2010-2014)
- Age 7 months-25 years
- 20 diagnostic categories (non-CNS, solid tumors)
- Comprehensive multi-omics exome germline & tumor, RNAseq tumor & Illumina Omni SNP arrays of tumor

Definitions: Actionable

Definitions: Actionable

- **Actionable germline mutation:** loss of function mutation or known hotspot activating mutation of a cancer consensus gene or pathogenic or likely pathogenic mutation of an American College of Medical Genetics (ACMG) Gene
- **Actionable somatic mutation:** genomic alterations that changes the patient's diagnosis, or may be targeted with FDA approved drugs or in the context of existing clinical trials according to the NCI-adult MATCH-Criteria

Integrated landscape



Multi-Omics Integrated Landscape

RNAseq
Diagnostic, Driver, Actionable

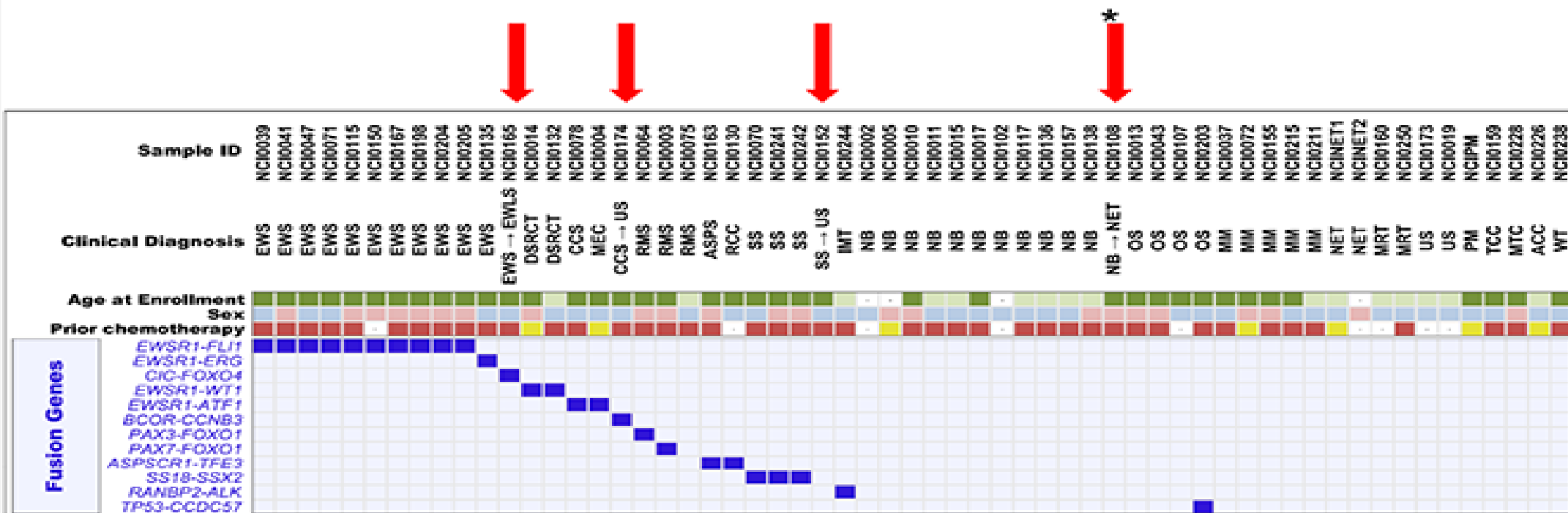
DNAseq and RNAseq
Somatic: Driver, Actionable

DNA copy number & RNAseq
Somatic: Driver, Actionable

DNAseq
Germ line: Disease causing,
Actionable

Fusion genes

Presence or absence of fusion genes and/or expression profiles confirms diagnosis or leads to revision of diagnosis



Pediatric germline mutations

~10% of Pediatric and Adolescent Young Adults with Cancers have Actionable Germline Mutations

Table 1. Germline mutations in American College of Medical Genetics (ACMG) reportable genes and tumor suppressor genes identified in 7 patients

Sample	Diagnosis	Gene	Mutation	Disease	Hotspot	Notes	Reportable by Strict ACMG Criteria
NCI0072	MM	<i>ATM</i>	p.Y380fs	Ataxia-Telangiectasia and cancer predisposition syndrome	No	Frameshift insertion of tumor suppressor gene	Yes
NCI0010	NB	<i>BRCA1</i>	Q1313X	Hereditary breast and ovarian cancer syndrome	Yes	Pathogenic, reportable	Yes
NCI0010	NB	<i>PMS2</i>	p.K356fs	Lynch syndrome and mismatch repair cancer syndrome	No	Frameshift deletion of tumor suppressor gene	Yes
NCINET2	NET	<i>PTEN</i>	p.R14fs	PTEN Hamartoma tumor syndrome	No	Frameshift deletion of tumor suppressor gene	Yes
NCI0228	MTC	<i>RET</i>	M918T	Multiple endocrine neoplasia 2B	Yes	Pathogenic, reportable	Yes
NCI0152	SS → US	<i>TP53</i>	R175H	Li-Fraumeni syndrome	Yes	Patient tumor has LOH of wild-type tp53 on other allele	No
NCI0226	ACC	<i>TP53</i>	A159K	Li-Fraumeni syndrome	Yes	Tumor has LOH of wild-type tp53 on other allele, novel, 2 base non-frameshift substitution, c.358_359delGinsTT	No
NCI0211	MM	<i>TSC1</i>	p.S828R	Tuberous sclerosis type 1, lymphangioleiomyomatosis, focal cortical dysplasia, and everolimus sensitivity	No	Nonsynonymous SNV, autosomal dominant, patient also has a germline TSC2 mutation	No
NCI0211	MM	<i>TSC2</i>	p.T246A	Tuberous sclerosis type 2, and lymphangioleiomyomatosis	Yes	Nonsynonymous SNV, autosomal dominant, patient also has a germline TSC1 mutation	No

NOTE: Mutations were confirmed by direct visualization on an IGV viewer, and by Sanger sequencing.

Abbreviations: ACC, adrenocortical carcinoma; MM, malignant melanoma; MTC, medullary thyroid carcinoma; NET, neuroendocrine tumor; RMS, rhabdomyosarcoma; SS, synovial sarcoma; US, undifferentiated sarcoma; horizontal arrow indicates change in diagnosis.

Actionable somatic mutations

Approximately 50% (30/59) of Pediatric and Adolescent Young Adults with Cancers Have Actionable Somatic Mutations

Table 2. Summary of actionable mutations in relapsed and refractory pediatric solid tumors

Sample	Diagnosis	Gene	Stage	Modality	Mutation	AA Change	Level	Drug	Clinical trial: Pediatric	FDA-Approval in adults	Exact mutation vs. hotspot	Reference preclinical data for level 3
NC00037	MM	BRAF	Relapsed	WES/WTS	NS SNV	p.V600E	1	Vemurafenib, dabrafenib	Yes	Yes	Exact	—
NC00072	MM	BRAF	Diagnostic	WES/WTS	NS SNV	p.V600E	1	Vemurafenib, dabrafenib	Yes	Yes	Exact	—
NC00215	MM	BRAF	Relapsed	WES/WTS	NS SNV	p.V600E	1	Vemurafenib, dabrafenib	Yes	Yes	Exact	—
NC00655	MM	GNAQ	Relapsed	WES/WTS	NS SNV	p.Q209L	1	Temsirolimus, trametinib, vorinostat	No	Yes	Exact	—
NC00002	NS	ALK	—	WES/WTS	NS SNV	p.R3273G	2a	Crizotinib	Yes	Yes	Exact	—
NC00010	NS	ALK	Relapsed	WES/WTS	NS SNV	p.F1174V	2a	Crizotinib	Yes	Yes	Exact	—
NC00017	NS	ALK	Relapsed	WES/WTS	NS SNV	p.F1174L	2a	Crizotinib	Yes	Yes	Exact	—
NC00038	NS	ALK	Relapsed	WES/WTS	NS SNV	p.Y1278S	2a	Crizotinib	Yes	Yes	Exact	—
NC00244	HT	ALK	Relapsed	WTS	MLL2-ALK fusion	—	2a	Crizotinib	No	Yes	Exact	—
NC00244	HT	ALK	Relapsed	WES/WTS	NS SNV	p.R177T	2a	Crizotinib	No	Yes	Exact	—
NC00215	MM	GNAI1	Relapsed	WES/WTS	NS SNV	p.S268F	2a	Trametinib	No	Yes	—	—
NC00043	EWS	CDK	Relapsed	WES/WTS	NS SNV	p.R132C	2a	IDH1 inhibitors	No	No	Exact	—
NC00075	RMS	PIK3CA	Relapsed	WES/WTS	NS SNV	p.P104G	2a	PI3K/AKT/mTOR inhibitors	Yes	Yes	Exact	—
NC00067	EWS	PIK3CA	Refractory	WES/WTS	NS SNV	p.D1047G	2a	PI3K/AKT/mTOR inhibitors	Yes	Yes	Exact	—
NC00013	OS	PTEN	Relapsed	WES/WTS	Frameshift deletion	p.K80fs	2a	PI3K/AKT/mTOR inhibitors	Yes	No	—	—
NC00012	NET	PTEN	—	WES/WTS	Germline frameshift deletion/autosomal LOH	p.R58fs	2a	PI3K/AKT/mTOR inhibitors	Yes	No	—	—
NC00028	HTC	RET	Relapsed	WES/WTS	Germline SNV	p.M591T	2a	Vandetanib	Yes	Yes	Exact	—
NC00017	NS	CDKN2A	Relapsed	SNP Array/WTS	Homozygous loss	—	3	CDK4/6 inhibitor	No	No	—	36
NC00071	EWS	CDKN2A	Relapsed	SNP Array/WTS	Homozygous loss	—	3	CDK4/6 inhibitor	No	No	—	36
NC00012	NET	CDKN2A	—	SNP Array/WTS	Homozygous loss	—	3	CDK4/6 inhibitor	No	No	—	36
NC00011	NS	MYCN	Relapsed	SNP Array/WTS	Amplification	—	3	Biomimetic inhibitors	No	No	—	37
NC00075	RMS	MYCN	Relapsed	SNP Array/WTS	Amplification	—	3	Biomimetic inhibitors	No	No	—	37
NC00002	NS	MYCN	—	SNP Array/WTS	Amplification	—	3	Biomimetic inhibitors	No	No	—	37
NC00036	NS	MYCN	Relapsed	SNP Array/WTS	Amplification	—	3	Biomimetic inhibitors	No	No	—	37
NC00038	WT	MYCN	Relapsed	WES/WTS	NS SNV	p.P44L	3	Biomimetic inhibitors	No	No	—	37, 38
NC00050	MRE	SMARCB1	—	SNP Array/WTS	Homozygous loss	—	3	CDK2 inhibitors	No	No	—	39, 40
NC00050	MRE	SMARCB1	Refractory	WES/WTS	NS SNV	p.R40X	3	CDK2 inhibitors	No	No	—	39, 40
NC00047	EWS	STAT2	Relapsed	WES/WTS	NS SNV	p.E594K	3	PAOP inhibitors	Yes	No	—	41
NC00050	EWS	STAT2	—	WES/WTS	NS SNV	p.Q296K	3	PAOP inhibitors	Yes	No	Hotspot	41
NC00016	MM	PSC1	Relapsed	WES/WTS	NS SNV	p.S628R	3	Eveolimus	No	Yes	—	42
NC00016	MM	PSC2	Relapsed	WES/WTS	NS SNV	p.T245A	3	Eveolimus	No	Yes	—	42

NOTE: SNVs were confirmed by direct visualization on an Illumina MiSeq, and validation by Sanger sequencing or confirmation CLIA-certified laboratories.

Abbreviations: EWS, Ewing sarcoma; HT, epithelial inflammatory myofibroblastic sarcoma; MM, malignant melanoma; MRE, malignant rhabdoid tumor; HTC, medullary thyroid carcinoma; NS, neuroblastoma; NET, neuroendocrine tumor; OS, osteosarcoma; RMS, rhabdomyosarcoma; WT, Wilms tumor.

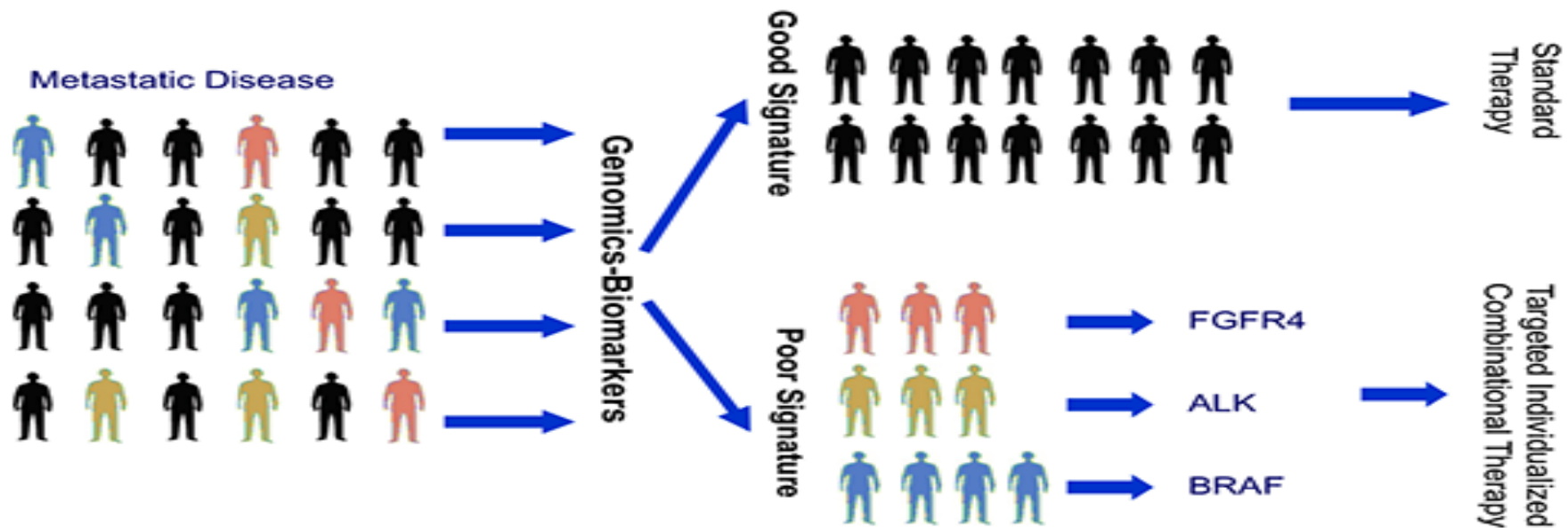
Summary

Summary

- **Demonstrated the importance and feasibility of performing multi-dimensional ClinOmics in the clinical setting in real time**
- **~50% of children with pediatric or AYA patients with relapsed or refractory cancers have actionable somatic mutations**
- **~ 10% have actionable germline mutations. Importance of performing parallel germline sequencing; some therapeutically actionable (e.g. DNA repair, PTEN, TSC1, TSC2, HRAS, RET, ALK)**

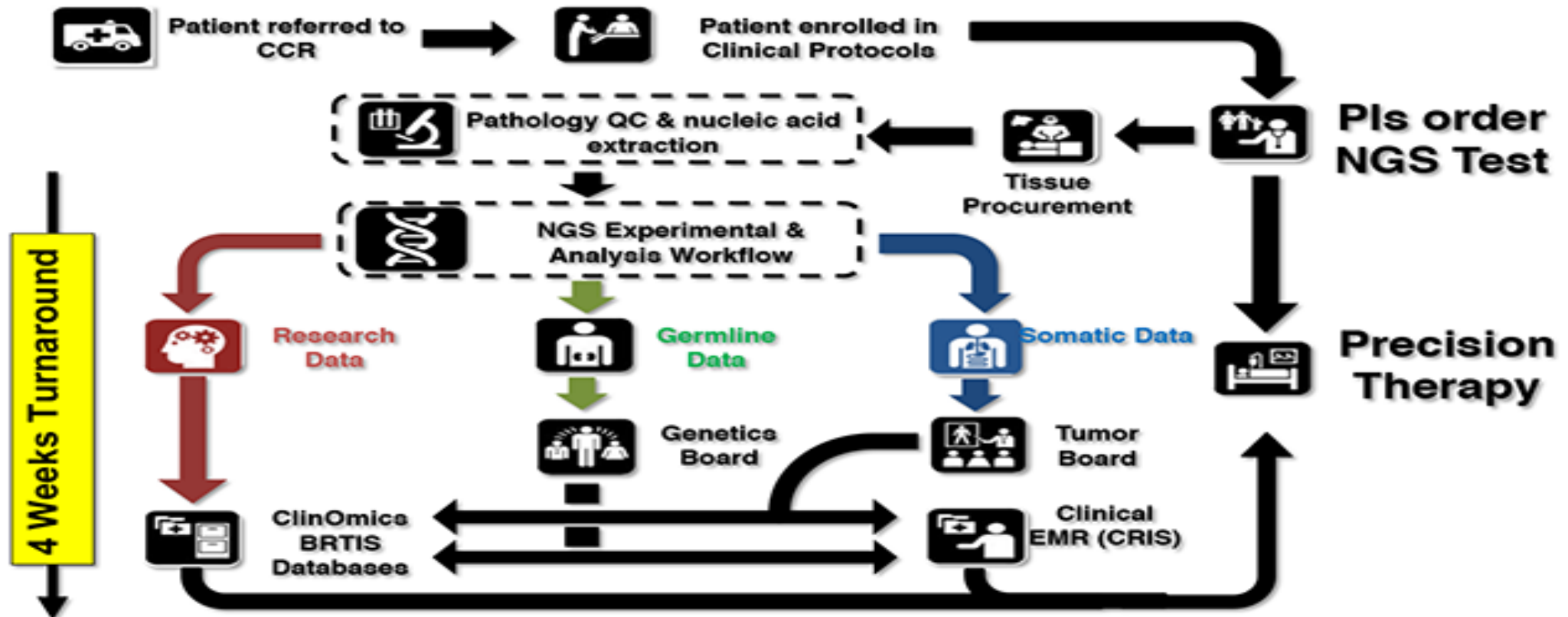
Precision medicine

Genomics Enables Precision Medicine



ClinOmics Program

CCR ClinOmics Program



Sequencing equipment

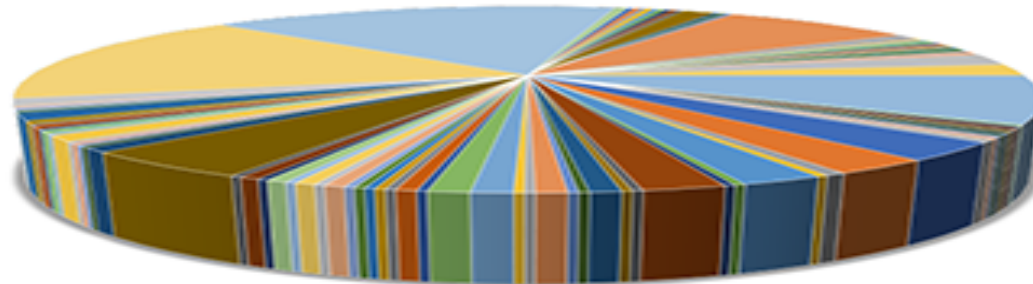
Sequencing Equipment



- Two NextSeq500s for speed and lower throughput
 - 65 Gb/run
 - 14 hours/run
- One HiSeq2500: for high throughput
 - 1000Gb/run
 - 32 exomes or transcriptomes
 - 14 days/run

Patient diagnoses

396 Patients of 93 diagnoses



- AEC
- Anaplastic Astrocytoma
- Anaplastic PTA
- Bladder cancer
- Cholangiocarcinoma
- Dermatofibrosarcoma protuberans
- Diffuse Intrinsic pontine glioma
- Ependymoma
- Gland Cell Ovarian carcinoma
- Grade 2 Oligodendroglioma
- Invasive well differentiated squamous cell carcinoma
- Lymphoblastoma
- Melanoma
- Mesothelioma Pleural
- Metastatic Pancreatic Neuroendocrine Carcinoma
- Multiple Rare Tumors
- Neuroblastoma 1
- Osteosarcoma
- Papillary tumor of the pineal region
- Poorly differentiated carcinoma (lung vs. thyroid)
- Renal cell carcinoma
- Small Cell Carcinoma of rectum
- Temporal high grade glioma
- Uveal melanoma

- Acute lymphoblastic leukemia
- Anaplastic Ependymoma
- Anaplastic Fibrous histiocytoma
- Breast cancer
- Chondroma
- Desmoid Fibromatosis
- Endometrial cancer
- Ewing's sarcoma
- Glioblastoma
- Hepatic Angiosarcoma
- Keratinocarcinoma
- Mastocytosis
- Merkel Cell Carcinoma
- Mesothelioma Pancreatic
- MPPNET
- Myxopapillary Ependymoma
- Neuronal tumor
- Ovarian Serous Carcinoma
- Pilocytic Astrocytoma
- Prostate cancer
- Rhabdomyosarcoma
- Small Cell Carcinoma of the ovary hypercalcemic type (SOCCOT)
- Teratoma

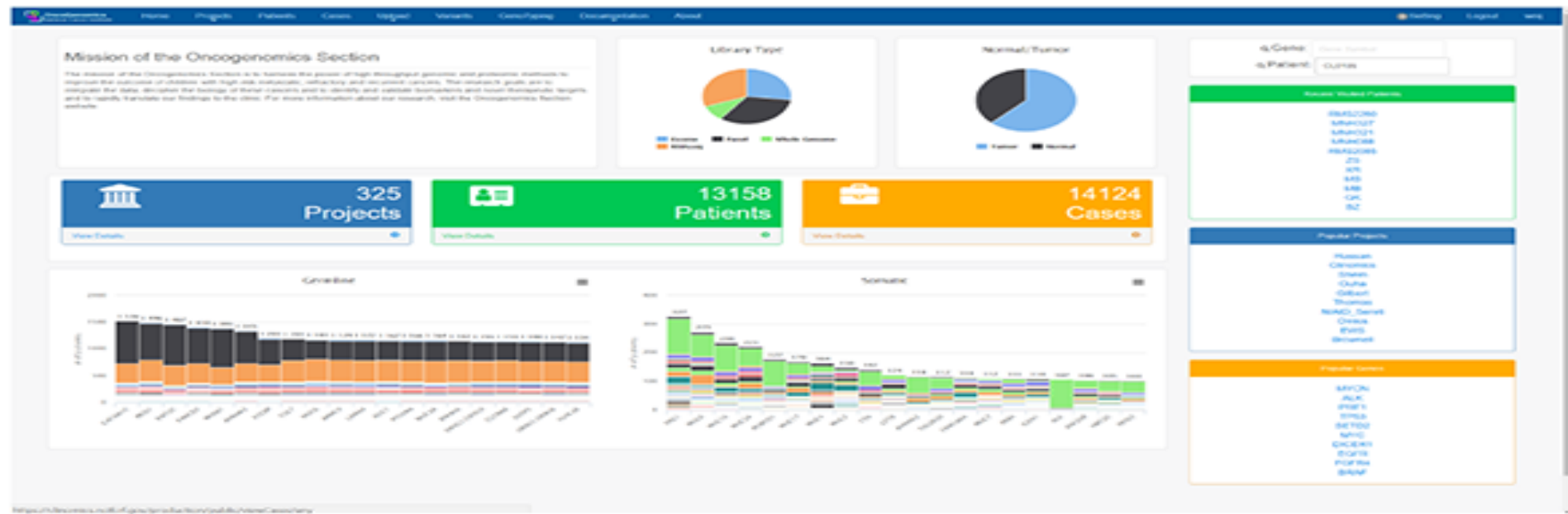
- Acute myeloid leukemia
- Anaplastic meningioma
- Astrocytoma
- Carcinoid, BRCA1 positive
- Clear cell sarcoma
- Desmoplastic small round cell tumor
- Endometrial Stromal Sarcoma
- Extracranial Small Cell Cancer
- Glioma
- Hepatocellular cancer
- Left Cerebellar Sarcoma
- Medullary Thyroid Cancer metastatic
- Mesothelioma
- Metastatic Anal Carcinoma
- Multinodular and Vasculating Neuronal Tumor
- Neuroendocrine carcinoma
- Neuronal Teratoma
- Ovarian Teratoma
- Pilocytic Astrocytoma
- Recurrent glioblastoma
- SCLC
- Small cell endometrial
- Thyroid

- Ampullary cancer
- Anaplastic Oligodendroglioma
- Atypical Central Neurocytoma
- Carcinoma of the Pancreas
- Colon cancer
- Diffuse Astrocytoma, Grade II
- Eosinophilia
- Gallbladder cancer
- Gliosarcoma
- Hepatocellular carcinoma
- Lung Adenocarcinoma
- Medullary Sarcoma
- Mesothelioma Peritoneal
- Metastatic NET
- Multiple carcinoma
- Neuroendocrine Tumor
- NSCLC
- Pancreatic cancer
- Pleomorphic neurofibroma
- Recurrent Medulloblastoma
- Small cell bladder
- Synovial sarcoma
- Undifferentiated sarcoma

Data portal

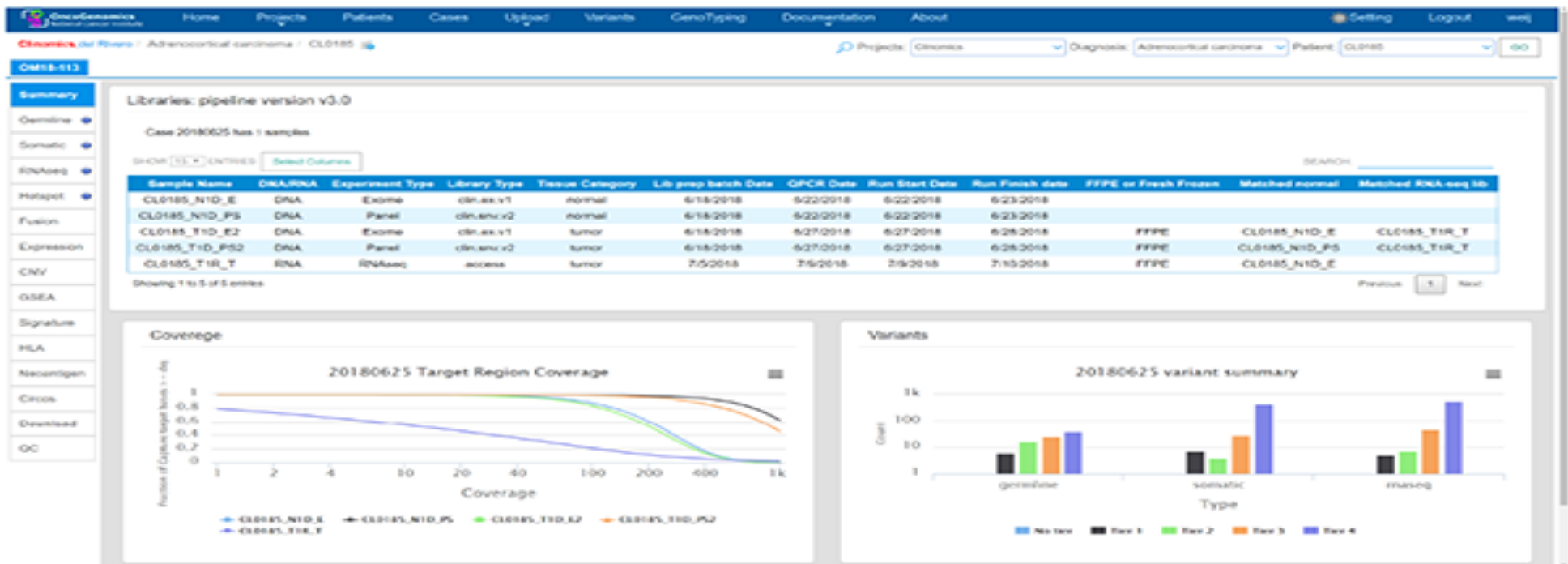
ClinOmics Data Portal

<https://clonomics.ncifcrf.gov/production/public/>



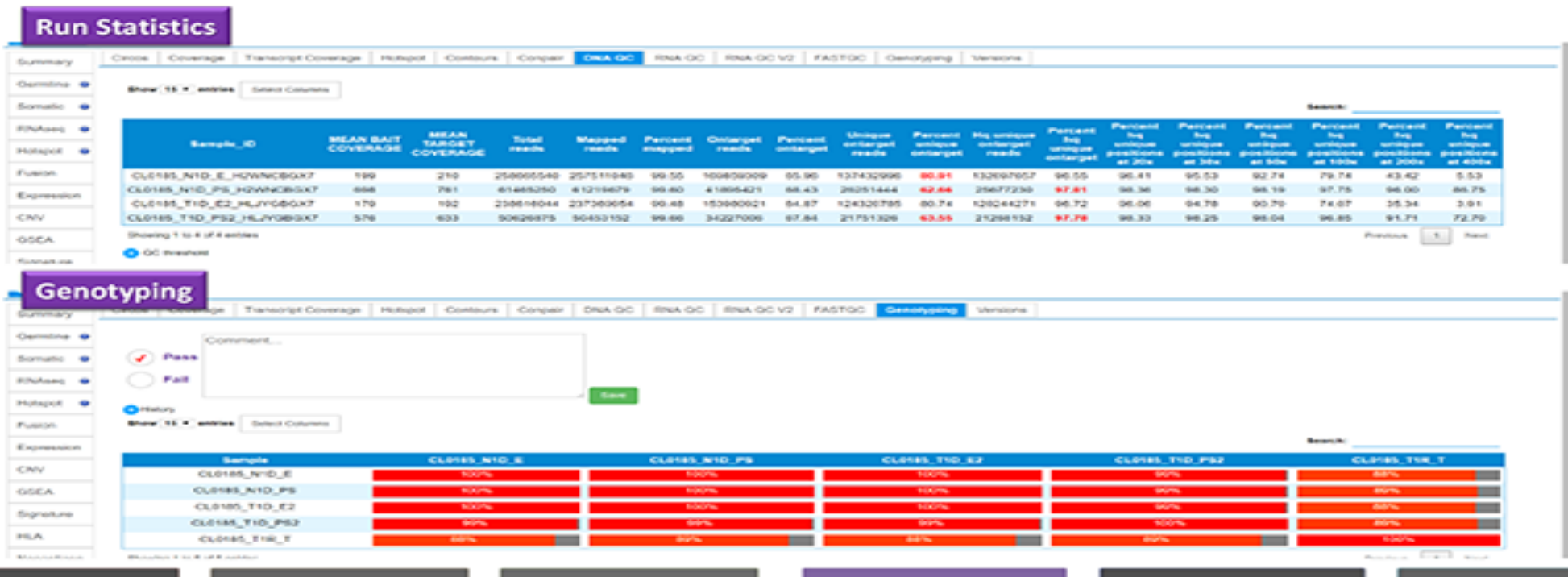
Patient summary

Patient Summary Page



QC report

QC Report: Sequencing Statistics & Genotyping



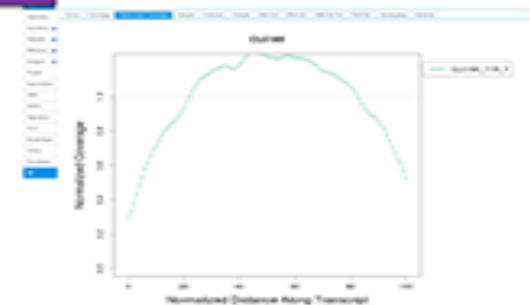
Coverage

QC Report: Coverage

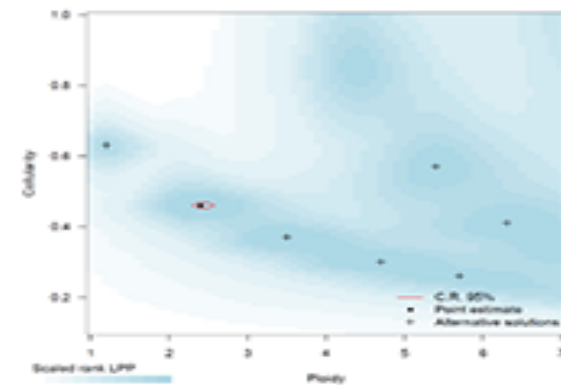
Circos



RNA Coverage



Tumor Content



Hotspot Coverage



Mutations

Germline and Somatic Mutations

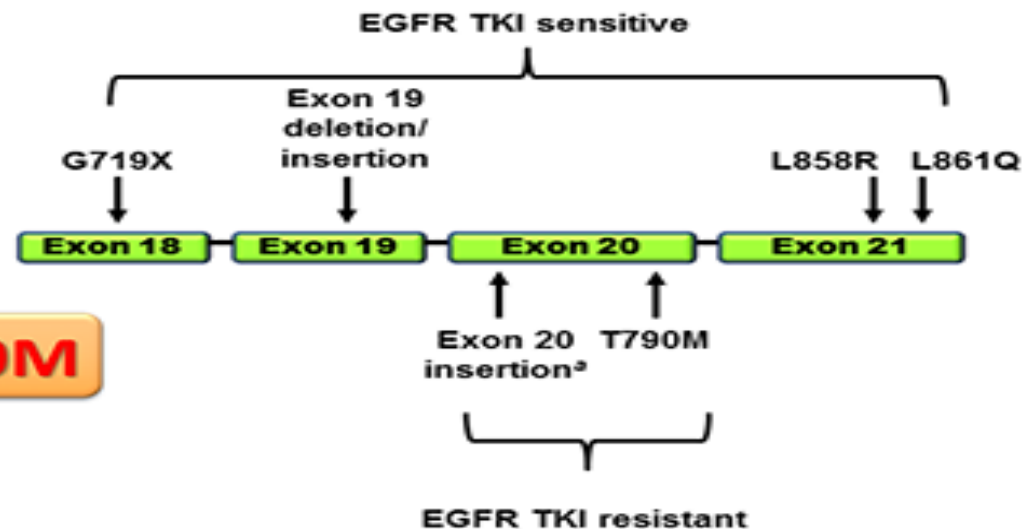
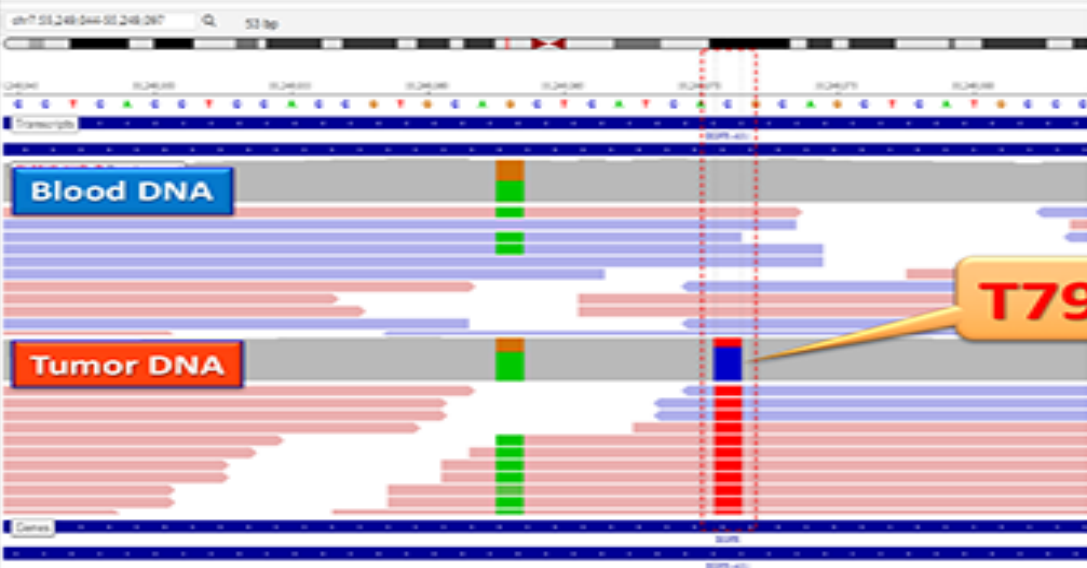
EGFR mutations

EGFR mutations in NSCLC

GV view of patient: CL0040 case: OM16-007 Total 4 sample(s)

(c: (check sample to load))

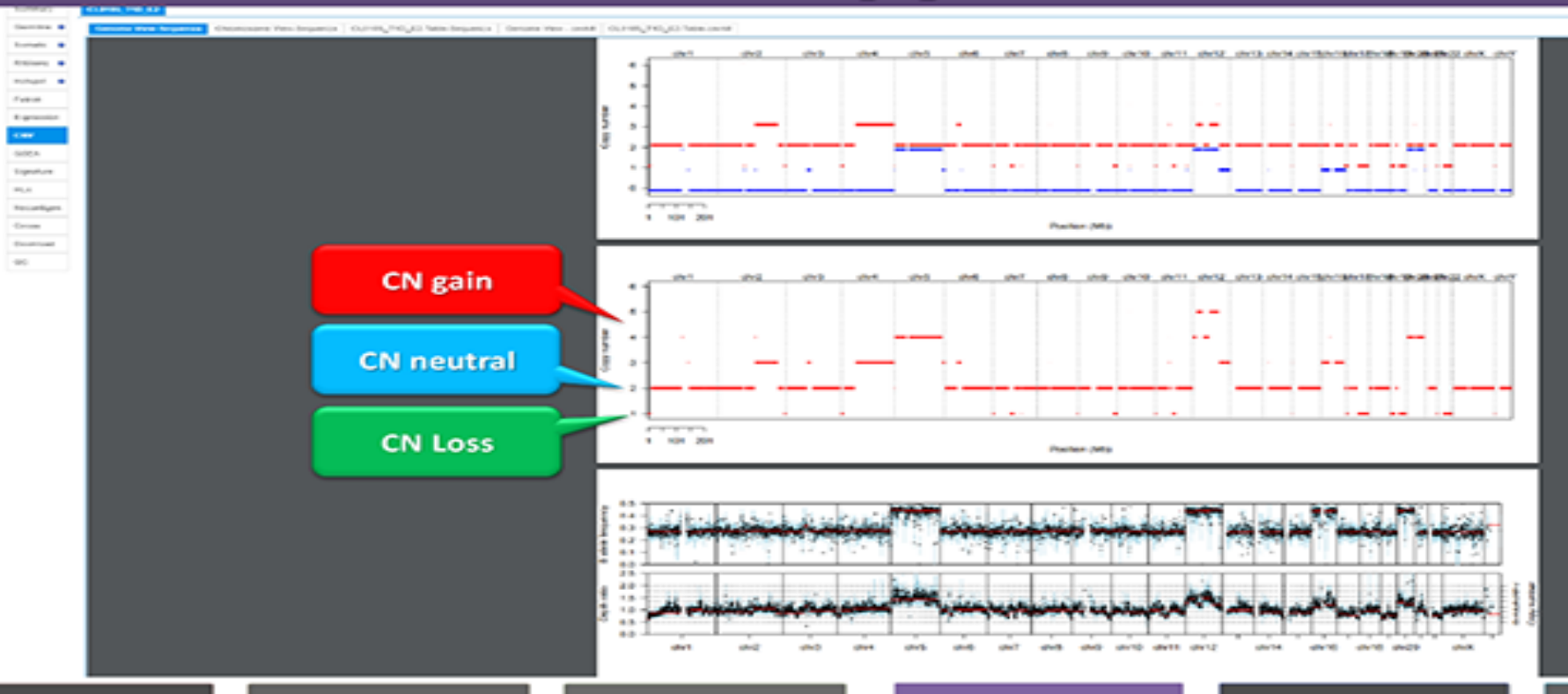
CL0040_N1D_E Exome, normal (Exome, normal) CL0040_T1D_E Exome, tumor (Exome, tumor) CL0040_N1D_P Panel, normal (Panel, normal) CL0040_T1D_P Panel, tumor (Panel, tumor)



<https://www.mycancergenome.org/content/disease/lung-cancer/egfr/>

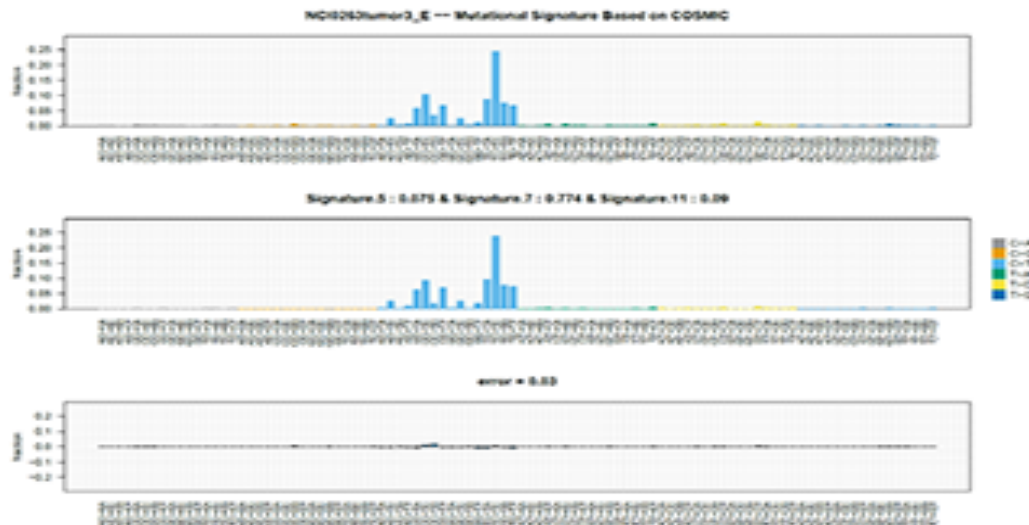
Tumor copy number

Tumor Copy Number

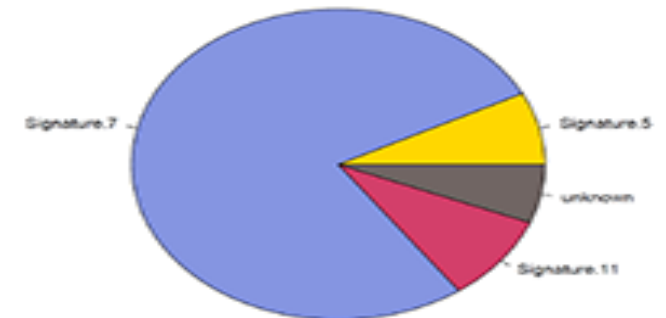


Mutation signatures

Mutation Signatures for Tumor



NCI0263: Melanoma



COSMIC (<https://cancer.sanger.ac.uk/cosmic/signatures>)

Signature 7



Cancer types: Signature 7 has been found predominantly in skin cancers and in cancers of the lg categorized as head and neck or oral squamous cancers.

Proposed aetiology: Based on its prevalence in ultraviolet exposed areas and the similarity of the mutational pattern to that observed in experimental systems exposed to ultraviolet light Signature 7 is likely due to ultraviolet light exposure.

Additional mutational features: Signature 7 is associated with large numbers of CC>TT dinucleotide mutations at dipyrimidines. Additionally, Signature 7 exhibits a strong transcriptional strand bias indicating that mutations occur at pyrimidines (i.e., by formation of pyrimidine-pyrimidine photodimers) and these mutations are being repaired by transcription-coupled nucleotide excision repair.

Comments: N/A

Signature 7: UV signature

Mutation burden

Mutation Burden

The screenshot displays the OncoGenomics National Cancer Institute web application. The top navigation bar includes links for Home, Projects, Patients, Cases, Upload, Variants, GenoTyping, Documentation, and About. A user is logged in as 'weij'. The breadcrumb trail shows 'Clinomics, del Rio' / 'Adrenocortical carcinoma' / 'CL0185'. Below this, filters for Projects (Clinomics), Diagnosis (Adrenocortical carcinoma), and Patient (CL0185) are shown with a 'GO' button. The left sidebar contains a list of analysis types: Summary, Germline, Somatic (selected), RNAseq, Hotspot, Fusion, Expression, CNV, GSEA, Signature, and HLA. The main content area is titled 'OM18-113' and shows tabs for 'Somatic-All', 'Somatic-CL0185_T1D_PS2-Panel', 'Somatic-CL0185_T1D_E2-Exome', and 'Mutation_Burden' (selected). A 'Callers' dropdown is set to 'MuTest'. A 'Records: 2/6' indicator is present. A 'Select Columns' button and a 'Show 15 entries' dropdown are also visible. A table displays the mutation burden data for two samples. The 'Burden Per MB' column for the second sample is highlighted with a red box. A search bar is located above the table. At the bottom of the table, it says 'Showing 1 to 2 of 2 entries (filtered from 6 total entries)' and includes 'Previous', '1', and 'Next' navigation buttons.

Diagnosis	Sample Name	Experiment Type	Caller	Burden	Total bases	Burden Per MB
Adrenocortical carcinoma	CL0185_T1D_E2	Exome	MuTest	612	45196537	13.54
Adrenocortical carcinoma	CL0185_T1D_PS2	Panel	MuTest	36	2465827	14.6

Fusion gene detection

Fusion Gene Detection from RNA-seq experiments



Genomic information

Other Useful Genomic Information

- **HLA typing (Tissue typing)**
- **Neoantigen prediction**
- **Gene expression**
- **Gene Set Enrichment Analysis (GSEA)**
- **Survival analysis if outcome data is available**

Conclusions

Conclusions

- Next generation sequencing (including whole genome, exome, and transcriptome) determines the complete genomic and epigenetic portrait of cancers at the base pair level
- Integrated analyses of the cancer can identify biologically relevant diagnostic, prognostic biomarkers and novel targets for precision medicine

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